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ASSESSMENT PLAN

For

CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

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For the

American Chemistry Council's
Acetic Acid and Salts Panel

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I. INTRODUCTION

The High Production Volume (HPV) Challenge Program is a voluntary initiative of the U.S. chemical industry to complete hazard data profiles for approximately 2800 HPV chemicals as identified on the U.S. Environmental Protection Agency's (USEPA) 1990 Toxic Substances Control Act (TSCA) Inventory Update Rule (IUR). In the U.S., HPV chemicals are those that are manufactured or imported in quantities greater than 1 million pounds per year. The hazard data to be provided in the program are those that meet the requirements of the Organization for Economic Cooperation and Development (OECD) Screening Information Data Set (SIDS) Program (OECD 1997a). SIDS, which has been internationally agreed to by member countries of the OECD, provides the basic screening data needed for an initial assessment of the physical-chemical properties, environmental fate, and adverse human and environmental effects of chemicals. The information for completing the SIDS can come from existing data or may be generated as part of the HPV Challenge Program. Once the available studies are identified or conducted, "robust summaries" are prepared.

The USEPA, industry, and Non-Governmental Organizations (NGOs) are unified in their commitment to minimize the numbers of animals tested in the HPV Challenge Program whenever it is scientifically justifiable (USEPA 1999a, 1999b). One approach is to evaluate closely related chemicals as a group, or category, rather than solely as individual chemicals. The use of categories in the HPV Challenge Program is encouraged by USEPA. Appropriately constructed categories allow for a more efficient evaluation while reducing the number of animals required for testing.

Accordingly, the American Chemistry Council (Council) (formerly the Chemical Manufacturers Association) Acetic Acid and Salts Panel (Panel) is sponsoring a category that includes several carboxylic food acids and their salts. This category previously was referred to as the Acetic Acid and Salts category. The Panel is comprised of the following companies:

A.E. Staley Manufacturing Company
Millennium Chemicals Incorporated
Cargill, Inc.
Archer Daniel Midland Company
The Procter and Gamble Company
Vulcan Chemicals
W.R. Grace & Company
Mallinckrodt Inc.
Eastman Kodak Company
Eastman Chemical Company
Sterling Chemicals
Celanese Ltd
OMG Americas, Inc.
The Shepherd Chemical Company

This assessment plan provides a summary and analysis of the available data, and identifies any unavailable data areas in the SIDS data profile. Section II of this assessment plan

provides a rationale and justification for the Carboxylic Food Acids and Salts category. Section III reviews the methods used in the collection of published and unpublished data. Section IV reviews the evaluation of data quality. Section V reviews the preparation of the robust summaries and the construction of a data matrix. Section VI is an in-depth evaluation of data matrix patterns for each of the four data endpoint categories (i.e., physical-chemical properties, environmental fate, ecotoxicity and toxicity). Section VII is a summary of the Carboxylic Food Acids and Salts category and its properties. Section VIII presents conclusions regarding data availability and addresses whether there is a need for additional testing to complete the SIDS profiles for the sponsored compounds.

II. IDENTIFICATION OF THE STRUCTURE BASED CATEGORY

The Panel is sponsoring a total of 13 individual compounds, the structures of which are shown in Appendix 1. As noted above, that this category was previously referred to as the Acetic Acid and Salts category, however, several of the comments received on the draft assessment plan suggested confusion as to the overall structure of the category. For clarification, therefore, the category has been renamed the Carboxylic Food Acids and Salts category to more clearly represent the relationship of the chemicals being sponsored. The category includes several food acids and their corresponding salts, specifically acetic acid and its ammonium, calcium, potassium, sodium, magnesium, and manganese salts; citric acid and its sodium, tripotassium and trisodium salts; fumaric acid; and malic acid[1]. While all 13 compounds are included under the umbrella of a single carboxylic food acids and salts category, they actually fall into four separate subcategories for data evaluation purposes based on their primary acid constituent. The data for these four subcategories (acetic acid and its salts; fumaric acid; malic acid; and citric acid and its salts) are generally evaluated independently from the other subcategories.

These compounds are grouped together because of their close structural relationships, their natural occurrence in plants and animals, and their role in cell metabolism, particularly in the tricarboxylic acid cycle (also known as the citric acid or Kreb's cycle), which is where humans get their energy. These compounds are all carboxylic acids or their respective salts. As shown in Appendix 1, acetic acid has one, fumaric acid and malic acid have two, and citric acid has three carboxylic acid functional groups. Malic acid and citric acid also have an additional alcohol group.

Role in the Citric Acid Cycle

Food acids, such as acetic acid, citric acid, fumaric acid, and malic acid (and citrate, fumarate and malate), are found in a wide variety of unprocessed foods. These acids are naturally occurring in the body in that they play key roles in the metabolic energy system called the Citric Acid cycle (Gardner 1966). This cycle consists of a series of chemical reactions occurring within the cell that are responsible for the final breakdown of food molecules to

[1] Note that the salts may be referred to by synonyms in some sources. For example, acetic acid ammonium salt is commonly called ammonium acetate. Similarly, citric acid tripotassium salt is commonly called potassium citrate or tripotassium citrate.

form carbon dioxide, water, and energy. This process is active in all animals and higher plants and is carried out in the mitochondria. While additional ingestion of these materials may not be incorporated into the tricarboxylic acid cycle directly, the fact remains that they occur naturally in the body.

In summary, the compounds in this category are naturally occurring in foods and essential to normal metabolic processes. They are also commonly used as flavor and texture enhancers in a wide variety of foods. The compounds in this category can be viewed as biochemically and toxicologically equivalent to their naturally occurring counterparts.

III. COLLECTION OF PUBLISHED AND UNPUBLISHED DATA

Panel members contributed in-house studies of physical-chemical properties, environmental fate and transport, ecotoxicity, and mammalian toxicity for the compounds in the category. To supplement the industry data, literature searches were conducted of on-line databases and CD-ROMs (e.g., Hazardous Substance Data Bank [HSDB], Registry of Toxic Effects of Chemical Substances [RTECS], Aquatic Toxicity Information Retrieval [AQUIRE]), standard scientific compendia (e.g., *CRC Handbook of Chemistry and Physics*, *The Merck Index*, *Patty's Industrial Hygiene and Toxicology*, *Handbook of Environmental Data on Organic Chemicals*, British Industrial Biological Research Association [BIBRA] toxicology profiles), and other published sources (e.g., International Uniform Chemical Information Database [IUCLID]). The literature search was augmented by investigating the web sites of a variety of government and regulatory organizations such as the U.S. Agency for Toxic Substances and Disease Registry (USATSDR), U.S. Consumer Product Safety Commission (USCPSC), U.S. Food and Drug Administration (USFDA), and World Health Organization (WHO). The USEPA ECOTOX database was also searched. A number of primary references from peer reviewed published journals were also reviewed. The Syracuse Research Corporation EPIWIN v.3.10 model, which is accepted by the USEPA for organic compounds, was used to provide estimates of key physical-chemical properties for some of the compounds.

IV. EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general USEPA and OECD SIDS guidance (USEPA 1999c; OECD 1997b) and the systematic approach described by Klimisch et al. (1997). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. The Klimisch et al. (1997) approach specifies four categories of reliability for describing data adequacy. These are:

1 **Reliable without Restriction:** Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

2 **Reliable with Restrictions:** Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

3 **Not Reliable:** Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

4 **Not Assignable:** Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

Only those studies which are deemed reliable for the current HPV Challenge Program purposes are included in the data set for this assessment plan. Reliable studies include both categories rated 1 (Reliable without restriction) and rated 2 (Reliable with restrictions). Studies rated 3 (Not reliable) were not used. Studies rated 4 (Not assignable) were used when professional judgment deemed it appropriate as part of a weight-of-evidence approach. Finally, some older studies were not included if they had been superceded by more recent studies rated 1.

V. ROBUST SUMMARIES AND CONSTRUCTION OF DATA MATRIX

Robust summaries were prepared according to the format recommended by the USEPA (1999d) and OECD (1997a) and constructed using Microsoft Word® software. These summaries present the salient information from each of the reliable studies. All of the summaries are collected into a dossier that includes all of the individual acids and salts for the category. The dossier for the Carboxylic Food Acid and Salts category is a separate document, which should be used in conjunction with this assessment plan.

The data in the robust summaries are used to construct a data matrix table. This table (Appendix 1 to this assessment plan) is a matrix of SIDS/HPV endpoints and the available data for each of the sponsored compounds in the Carboxylic Food Acid and Salts category. To facilitate the connection between data in the table and the corresponding robust summaries, reference sources have been included with each data point.

VI. EVALUATION OF MATRIX DATA PATTERNS

The data matrix table (Appendix 1) identifies where data for specific compounds and data endpoints are available (data provided) and not available (indicated by "—" in the table). The available data were evaluated for patterns and trends among the 13 compounds that could be used to predict values for a particular endpoint (e.g., acute oral toxicity) where adequate data are not available for a given compound (i.e., "Read Across"). In addition, the data were evaluated to determine to what extent the SIDS/HPV data endpoints were covered by available data for each compound in the category (i.e., "Read Down").

A. Evaluation of "Read Across" Patterns

The following discussion reviews the "Read Across" patterns within each subcategory for each of the four major data areas: physical-chemical properties, environmental fate and

transport, ecotoxicity, and mammalian toxicity. The primary patterns to identify in the physical-chemical property data are similarities in the parameters that affect dissociation and partitioning between aqueous and organic phases. In reviewing the environmental fate data, the important information to identify is the primary mechanism of degradation or dissociation of the compounds. These factors also affect the bioavailability and aquatic toxicity of the compounds. Similarly, it is important to identify any trends or similarities in the mammalian toxicity data, which are important surrogates for potential human effects. Each of the four acids (acetic, fumaric, malic, and citric), along with their corresponding salts, are reviewed separately in the following sections and "read across" patterns are evaluated within each subcategory.

Acetic Acid and its Salts

Acetic acid and its salts are comprised of seven compounds that include acetic acid ($H_4C_2O_2$), ammonium acetate ($H_7C_2NO_2$), calcium acetate ($H_6CaC_4O_4$), magnesium acetate ($H_6C_4MgO_4$), manganese acetate ($H_6C_4MnO_4$), potassium acetate ($H_3KC_2O_2$), and sodium acetate ($H_3NaC_2O_2$). The chemical structures, physical-chemical properties, environmental fate behavior, and aquatic and mammalian toxicity of these seven compounds are similar. Acetic acid and its salts undergo dissociation in aqueous media into the acetate anion ($H_3C_2O_2^-$) and the respective cations (H^+, NH_4^+, Ca^{2+}, Mg^{2+}, Mn^{2+}, K^+, Na^+). The toxicity of each compound is driven by acetate, with the cations in most cases playing a minor role.

Physical-chemical Properties

Reliable data exist for melting and boiling points, water solubility and pH for most of the seven compounds (see Appendix 1). With the exception of acetic acid, for which actual experimental data exist, octanol-water partition coefficient (Kow) and vapor pressure data are largely available as estimated values using the standard chemical property estimation software, EPIWIN v.3.10 (USEPA 2000). All seven compounds are highly water soluble and of moderate to low volatility. Based on such information, the Panel believes that the available data adequately characterizes the physical-chemical properties of acetic acid and its salts.

Environmental Fate and Transport

Reliable data for environmental fate and transport behavior are available for acetic acid and its salts (see Appendix 1). Biodegradation appears to be the most significant removal mechanism. These compounds readily dissociate into their respective cations and the acetate anion; the anion is subsequently biodegraded. Data indicate that acetic acid and sodium acetate (acetic acid, sodium salt) photodegrade, although the rate is substantially slower than that of biodegradation. Level III fugacity modeling predicts that about 55% of any acetic acid released to the environment would partition to air, 23% to water, 22% to soil, and <1% to sediments. These data demonstrate that acetic acid and its salts are not persistent in the environment. The Panel believes that the available data and analogous behavior of the other compounds can be used to

adequately characterize the environmental fate and transport properties of acetic acid and its salts.

Ecotoxicity

Reliable ecotoxicity data for aquatic animals are available for four of the seven compounds (see Appendix 1). The ecotoxicity data indicate that these compounds are practically nontoxic to only slightly toxic. The three remaining salts (calcium, magnesium and manganese) are closely related to the other salts in structure and behavior and so would be expected to have low toxicity as well. Of the seven compounds, acetic acid appears more toxic, which is attributable to its relatively low pH. Toxicity data for algae are available for acetic acid and its sodium salt, and also indicate generally low toxicity. While some unavailable data areas exist, the Panel believes that the available aquatic toxicity data and the generally low to moderate toxicity of acetic acid and its salts adequately characterize the ecotoxicity of these compounds.

Mammalian Toxicity

Several aspects of mammalian toxicity are evaluated. Acute testing provides information on gross effects, such as mortality, from exposure to high doses. Repeated dose testing provides information on toxicity associated with multiple doses over time. Genetic testing is conducted to evaluate the potential for mutagenic effects by using bacterial systems (e.g., the Ames test), non-bacterial systems (e.g., chromosomal aberrations), and *in vivo* (i.e., live animal) systems. Reproductive and developmental/teratogenic testing provides information on the potential effects of long-term exposure to lower doses, especially as related to possible effects in developing embryos and young animals. It is important to note that the lack of significant exposure may obviate the need to conduct mammalian testing.

The available data indicate that acetic acid and its salts have generally low acute mammalian toxicity (see Appendix 1). Acute oral toxicity data for mammals are available for all compounds with the exception of the ammonium salt. Acute inhalation data are available for acetic acid and the sodium salt. Inhalation is not expected to be a primary route of exposure given that acetic acid and its salts have generally low volatility and are highly soluble. Dermal toxicity data are available only for acetic acid, but the level of toxicity is low and the salts are expected to exhibit a comparable dermal safety profile. Several studies indicate that the acute toxicity via other routes of exposure (i.e., intravenous, subcutaneous, intraperitoneal, etc.) is also low. Thus, additional acute testing on the other compounds is not deemed by the Panel to be necessary to characterize this category.

There are repeated dose, genetic, and developmental/teratogenic toxicity test endpoints for acetic acid. An essentially complete set of data for the sodium salt of acetic acid is also available. Less data are available for the other salts, but the data that are available show similar responses to the sodium salt. The dissociative nature

of salts suggests that additional testing would provide no information useful for assessing the hazard of this category.

Data for the counter ions (metals) are extensive in the published literature. Well recognized and peer reviewed compendia (e.g., USATSDR Toxicological Profiles, WHO Environmental Health Criteria, NIOSH/OSHA Occupational Health Guidelines, ACGIH Documentation of TLVs, RTECS Toxicity Reports, etc.) are readily available to USEPA and other interested parties and therefore are not included with this submission. These compendia provide sufficient information for review of the metal counter ions. In general, the counter ions are not expected to impact the overall safety profile of the salts within the Carboxylic Food Acids and Salts category.

The manganese ion may be a special case because of its potential neurotoxicity. The available data indicate that the acute toxicity of the manganese salt is very similar to the other salts of acetic acid (rat oral LD_{50} = 3,730 mg/kg). Results of a repeated dose study in which mice were given a relatively high dose of the manganese salt (2 g Mn/kg food) indicate some effects including body weight gain suppression, changes in biomarkers indicative of potential neurotoxicity effects, and accumulation of manganese in the hypothalamus (Komura and Sakamoto 1992). Results of a rec-assay genotoxicity study indicated a weakly positive response for the manganese salt (Nishioka 1975). However, based on the weak response in this non-standard assay, it is unclear whether the manganese salt would exhibit mutagenicity. Abnormalities were observed in chick embryos following injection of the manganese salt directly into eggs (Verrett et al. 1980), however the usefulness of this non-standard study in assessing developmental toxicity are questionable. Overall, the available data suggest that high doses of the manganese salt of acetic acid may affect toxicity to a greater extent than the other cations. However, it is important to note that the potential for exposure to the manganese acetate salt is very low. This material is used as a catalyst in the manufacture of plastics and would not reach consumers in normal conditions. Industrial exposure is minimal and limited by the use of normal industrial engineering controls, safe work practices, and personal protective equipment.

Acetic acid is naturally occurring as the acid in apple cider vinegar and other fruit-derived products. It and several of its salts are commonly used as food additives (e.g., as flavor enhancers) and are listed as Generally Recognized as Safe (GRAS) by the U.S. Food and Drug Administration (USFDA). Given the general lack of significant toxicity, the natural occurrence in both plants and animals, and the common use in foods, the Panel believes that no additional mammalian toxicity testing is necessary to fulfill the scope of the HPV Challenge Program.

Fumaric Acid

While acetic acid is the simplest form and contains only a single carboxylic acid unit, fumaric acid contains two carboxylic acid units connected by a double bond.

Physical-chemical Properties

Reliable data are available for all of the SIDS/HPV data elements and indicate that fumaric acid is highly soluble in water and has low volatility. Level III fugacity modeling predicts that about 38% of any fumaric acid released to the environment would partition to water, 1% to air, 60% to soil, and <1% to sediments. The Panel believes that the available data adequately characterize the physical-chemical properties of fumaric acid.

Environmental Fate and Transport

Reliable data are available for all the SIDS/HPV data elements. Fumaric acid dissociates into H^+ and fumate ($H_3C_4O_4^-$) and fumate undergoes significant degradation by both biotic and abiotic mechanisms and is therefore not persistent. Nearly complete biodegradation was observed after 21 days under aerobic conditions. The Panel believes that the available data adequately characterize the environmental fate and transport properties of fumaric acid.

Ecotoxicity

Likewise, complete data are available for all the SIDS/HPV aquatic toxicity data elements. LC_{50} values for fish and *Daphnia* were greater than 200 mg/L. The value for the more sensitive algae was 41 mg/L. These data indicate that fumaric acid has low toxicity to aquatic animals and plants.

Mammalian Toxicity

Acute oral and dermal toxicity data indicate that fumaric acid is of low acute toxicity, with LD_{50} values from approximately 10 g/kg bw (oral) to greater than 20 g/kg bw (dermal). *In vitro* and in vivo studies were negative with regards to genetic toxicity. Reproductive and developmental/teratogenic toxicity studies also resulted in no indication of these effects after exposure to fumaric acid. The Panel believes that the large amount of available data and the low toxicity indicated are adequate to characterize the mammalian toxicity of fumaric acid.

In addition, fumaric acid is naturally occurring in apples, beans, carrots and other fruits and vegetables. It is also commonly used to control pH and produce light textures in such foods as cake, cookies and soft drinks. Fumaric acid and its salts are listed as food additives by the USFDA.

Malic Acid

Malic acid is very similar to fumaric acid, with the difference being the addition of a hydroxyl group (OH) and removal of a double bond.

Physical-chemical Properties

Reliable data are available for all of the SIDS data elements and indicate that malic acid is highly soluble in water and has a low volatility. Based on such information, the Panel believes that the available data adequately characterize the physical-chemical properties of malic acid.

Environmental Fate and Transport

Photodegradation and biodegradation data are available for malic acid and show that it dissociates into H+ and malate ($H_5C_4O_5^-$). Malate has been shown in a series of screening tests to biodegrade readily in soil and water. Level III fugacity modeling predicts that about 38% of any malic acid released to the environment would partition to water, <1% to air, 62% to soil, and <1% to sediments. Based on such information, the Panel believes that malic acid is not persistent in the environment and is adequately characterized.

Ecotoxicity

Data on the aquatic toxicity of malic acid to daphnids are available. No data on toxicity to fish and algae were available, but the 48 hour LC_{50} for *Daphnia magna* was 240 mg/L, indicating a low level of aquatic toxicity. Given this data and the considerable aquatic toxicity data for the structurally related compounds in the overall Carboxylic Food Acids and Salts category, no further aquatic tests are deemed to be necessary by the Panel.

Mammalian Toxicity

Acute data for the oral and intraperitoneal exposure routes are available for malic acid and indicate a low to moderate toxicity. Dermal toxicity data are not available for malic acid, but are expected to be comparable to the relatively low order of dermal toxicity associated with fumaric acid. Both in vitro and in vivo studies demonstrated no evidence of genetic toxicity. Developmental/teratogenic toxicity studies also resulted in no indication of these effects after exposure to malic acid. The Panel believes that the large amount of available data, combined with the low toxicity, are adequate to characterize the mammalian toxicity of malic acid.

In addition, malic acid occurs naturally as the major acid in apples, apricots, cherries, broccoli, carrots, potatoes, and many other fruits and vegetables. It is also commonly used as a flavor booster in candy, jelly, fruit drinks and ice cream. It is listed as GRAS by the USFDA.

Citric Acid and its Salts

Citric acid and its salts are comprised of four compounds, which include citric acid ($H_8C_6O_7$), sodium citrate ($H_7NaC_6O_7$), tripotassium citrate ($H_5K_3C_6O_7$), and trisodium citrate ($H_5Na_3C_6O_7$). The chemical structures and available data indicate that the physical-chemical properties, environmental fate behavior, and aquatic and mammalian toxicity of these four compounds are similar. As in the case of the other acids and salts in this category, citric acid and its salts undergo dissociation in aqueous media into the citrate anion ($H_7C_6O_7^-$) and the respective cations (K^+, Na^+). The toxicity of each compound is driven by citrate, with the cations playing a minor role. Therefore, where data are available for any of the compounds within this sub-category, they are considered by the Panel to be adequate to represent the entire group.

Physical-chemical Properties

Reliable data exist for all relevant physical-chemical properties for citric acid and its tripotassium and trisodium salts. These compounds are all highly water soluble and of moderate to low volatility. The Panel believes that the available data adequately characterize the physical-chemical properties of citric acid and its salts.

Environmental Fate and Transport

Data on the environmental fate of citric acid and its trisodium salt are available. These data indicate that citric acid and its salts dissociate into their respective cations and the citrate anion, which is subsequently biodegraded. Studies indicate that citric acid and its trisodium salt are readily biodegraded (90-98% degradation after 48 hours). Level III fugacity modeling predicts that about 38% of any citric acid released to the environment would partition to water, <1% to air, 62% to soil, and <1% to sediments. Therefore, the existing data indicates that citric acid and its salts are not persistent in the environment. Collectively, these data are adequate, in the Panel's opinion, to characterize the environmental fate and transport properties of the group.

Ecotoxicity

Aquatic toxicity data for fish, *Daphnia* and algae are available for citric acid and its trisodium salt and indicate that these compounds have very low toxicity. With LC_{50} values ranging from 120 to 1,526 mg/L, citric acid is considered to be of low aquatic toxicity. The toxicity that is exhibited is most likely attributed to pH. The salts exhibit even less toxicity. The Panel believes that the available data and the structural similarities adequately characterize the ecotoxicity of citric acid and its salts.

Mammalian Toxicity

The available data indicate that citric acid and its salts have generally low mammalian toxicity. Oral toxicity data for mammals are available for citric acid and its sodium

salt and demonstrate low toxicity. Dermal toxicity studies indicate that these compounds are moderate contact irritants. Acute toxicity from other routes of exposure (i.e., intravenous, subcutaneous, intraperitoneal, etc.) are available for all four of the citric acid and salts and confirm the low toxicity. Repeated dose studies available for citric acid and its sodium salt resulted in no adverse effects. *In vitro* bacterial studies were negative for genotoxicity for citric acid and its sodium and tripotassium salts. An *in vivo* cytogenetics study with citric acid also indicated no genetic toxicity. Finally, reproductive and developmental/teratogenic data are available for citric acid and its sodium salt. While body weight and survival time were effected at high doses of citric acid, no reproductive, developmental or teratogenic effects were observed in tests with either the citric acid or its sodium salt. The Panel believes that the available data and analogous structures and behaviors are adequate to characterize the toxicity for citric acid and its salts.

Unlike the other acids and salts included in the category, citric acid and its salts are strong chelating agents. Evidence suggests that citric acid may reduce the physiological availability of calcium and iron. Other studies suggest that dietary citric acid and its salts may enhance calcium absorption and excretion and may also increase the absorption and retention of ingested metals such as aluminum, tin, cadmium and lead. While the chelating property of citric acid and its salts are evident, the available toxicological data indicate that these materials are not a significant concern to mammalian or human health. Indeed, the recent SIDS Initial Assessment Report and the BIBRA document both conclude that citric acid and its salts are not a significant concern.

In addition, citric acid occurs naturally in all citric fruits, beans, tomatoes, and many other fruits and vegetables. It is also listed as GRAS by the USFDA and is one of the most widely used food additives, with uses in everything from soft drinks to cheese.

B. Evaluation of "Read Down" Patterns

The "Read Down" patterns were considered among the four major data areas (physical-chemical properties, environmental fate and transport, ecotoxicity, and mammalian toxicity) for each of the 13 compounds. Complete data sets are available for the acetic, fumaric, malic and citric acids. Several of the salts of these acids also have relatively complete data sets. The category is characterized by acids and their salts, all of which readily dissociate in solution. This dissociation is followed by relatively rapid biodegradation and/or utilization in living organisms. The available data suggest that the cationic portion of the salt (e.g., Ca^{2+}, Mg^{2+}, K^{+}, Na^{+}) does not significantly affect the relative toxicity of these compounds. Based on the similarities in structure and behavior, the widespread natural occurrence in many fruits and vegetables, and the long history of use as food additives, the Panel believes that no further testing is necessary to predict the environmental fate, ecotoxicity or mammalian toxicity of these compounds.

VII. SUMMARY OF CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

The 13 compounds in the category are carboxylic food acids and their salts (acetic, fumaric, malic, citric). These compounds are grouped together because of their close structural relationships, their natural occurrence in plants and animals, and their fundamental role in cell metabolism, particularly in the tricarboxylic acid cycle (also known as the citric acid or Kreb's cycle), which is where humans get their energy. These compounds are all carboxylic acids or their respective salts. Most are listed as GRAS by the USFDA and have widespread use as food additives. Many of these compounds (Acetic acid, sodium salt; Citric acid and its sodium, tripotassium, and trisodium salts; and Fumaric acid) have been declared "minimal risk" by the USEPA as part of the recent tolerance reassessment process mandated under the Food Quality Protection Act of 1996.

Therefore, the Panel believes the available information supports the following conclusions. All of these acids and salts are highly water soluble and have low to moderate volatility. They dissociate readily in solution and biodegrade rapidly or are utilized in the body. They are not persistent in the environment.

These compounds all exhibit relatively low toxicity to aquatic organisms, with any toxicity observed related primarily to the effect of lowered pH. Likewise, these compounds all exhibit relatively low acute mammalian toxicity. Similarly, no significant effects were observed in genotoxicity, reproductive, and developmental/teratogenic testing.

Exposure from use as industrial chemicals to workers and consumers is minimal relative to that from use in applications regulated by the USFDA (e.g., food additives) and from consumption through natural sources in foods. Workplace exposures are limited through ACGIH and OSHA exposure guidelines and standard engineering controls and personal protective equipment.

VIII. CONCLUSIONS

The similarities in chemical structure and behavior of these 13 compounds, as well as the similarities found in the available testing data, support assessing these compounds under a single Carboxylic Food Acids and Salts category. The Panel believes that the available data sufficiently characterize the physical-chemical properties, environmental fate, ecotoxicity and mammalian toxicity of the group. In addition, these compounds have enjoyed widespread use as additives in a multitude of foods over many years and most are listed as GRAS by the USFDA. Many have also recently been listed as "minimal risk" in the USEPA tolerance reassessment process. Therefore, based on the available data, the structural similarities, the natural occurrence, and the lack of significant toxicity, the Panel believes that no further testing is necessary for the compounds included in this category to meet the requirements of the HPV Chemical Challenge Program.

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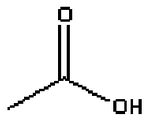
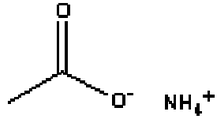
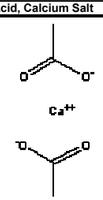
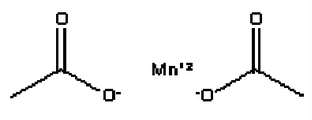
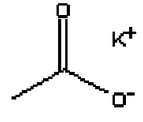
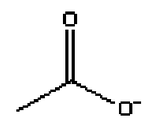
APPENDIX 1

SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

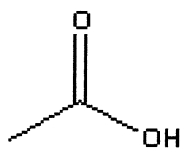
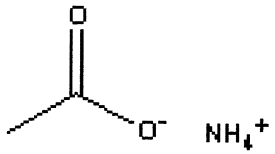
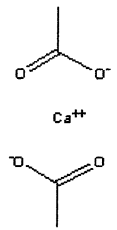
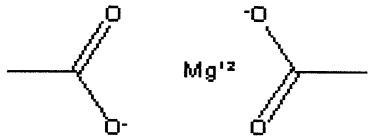
APPENDIX 1
SUMMARY DATA TABLE FOR ACETIC ACID AND SALTS CATEGORY

Description	Acetic Acid	Source	Acetic Acid, Ammonium Salt	Source	Acetic Acid, Calcium Salt	Source	Acetic Acid, Magnesium Salt	Source	Acetic Acid, Manganese Salt	Source	Acetic Acid, Potassium Salt	Source	Acetic Acid, Sodium Salt	Source
Structure														
CAS Number	64-19-7		631-61-8		62-54-4		142-72-3		638-38-0		127-08-2		127-09-3	
Physical-Chemical Properties														
Structural Formula	$H_4C_2O_2$		$H_7C_2NO_2$		$H_6CaC_4O_4$		$C_4H_6MgO_4$		$C_4H_6MnO_4$		$H_3KC_2O_2$		$H_3NaC_2O_2$	
Melting Point	16.7°C	Verschueren 1996	114°C	Verschueren 1996	--		80°C	Budavari 1996	--		292°C	Lewis 1994	58°C	Lewis 1994
Boiling Point	118.1°C	Verschueren 1996	--		Decomposes above 160°C	Budavari 1996	--		--		--		Decomposes above 400°C	Hoechst 1993
Vapour Pressure	11.4 mm Hg @ 20°C	Verschueren 1996	1.31×10^{-4} mm Hg @ 25°C	USEPA 2000 (calculated)	5.48×10^{-3} mm Hg @ 25°C	USEPA 2000 (calculated)	--		--		1.37×10^{-9} mm Hg @ 25°C	USEPA 2000 (calculated)	5.39×10^{-9} mm Hg @ 25°C	USEPA 2000 (calculated)
Octanol/Water Partition Coefficient (log)	-0.17	Verschueren 1996	-2.79	USEPA 2000 (calculated)	-1.38	USEPA 2000 (calculated)	-1.38	USEPA 2000 (calculated)	-0.58	USEPA 2000 (calculated)	-3.72	USEPA 2000 (calculated)	-3.72	USEPA 2000 (calculated)
Water Solubility	50 g/L @ 20°C	Verschueren 1996	1,480 g/L @ 4°C	Lide 1999	430 g/L @ 25°C	Verdugt 1992	Very soluble in water or alcohol	Budavari 1996	Soluble in water or alcohol	Budavari 1996	2,530 g/L	Lewis 1994	365 g/L @ 20°C	Hoechst 1993
pH Value, pKa Value	pH: 2.5 at 50 g/L and 20°C pKa: 4.76 @ 25°C	Hoescht 1994 Serjeant and Dempsey 1979	pH: 7.0 @ 350 g/L	Budavari 1996	pH: 7.6 @ 32 g/L	Budavari 1996	--		--		pH: 9.7 @ 98 g/L	Budavari 1996	pH: 7.5-9 @ 50 g/L , 20°C	Hoechst 1993
Fate and Transport														
Photodegradation	5.1×10^{-13} cm^3/molecule*sec 50% degradation after 21 days	Hoechst 1994 (calculated)	--		--		--		--		--		6.6% photomineralization after 17-h UV irradiation (> 290 nm)	Freitag et al. 1985
Stability in Water	Acids dissociate in water		Salts dissociate in water		Salts dissociate in water		Salts dissociate in water		Salts dissociate in water		Salts dissociate in water		Salts dissociate in water	
Biodegradation	Readily biodegradable: 99% after 7 days under anaerobic conditions using activated sludge	Kameya T. et al. 1995	Biodegrades in days to weeks	USEPA 2000 (calculated)	Readily biodegrades under aerobic conditions using activated sludge	Lohmann Unpublished	--		--		--		Inherently biodegradable: 100% after 5 days @ 160 mg/L under aerobic conditions using activated sludge Inherently biodegradable: 52.6% after 5 days @ 0.05 mg/L under aerobic conditions using activated sludge	Huels unpublished Freitag et al. 1985

APPENDIX 1
SUMMARY DATA TABLE FOR ACETIC ACID AND SALTS CATEGORY

Description	Acetic Acid	Source	Acetic Acid, Ammonium Salt	Source	Acetic Acid, Calcium Salt	Source	Acetic Acid, Magnesium Salt	Source	Acetic Acid, Manganese Salt	Source	Acetic Acid, Potassium Salt	Source	Acetic Acid, Sodium Salt	Source
Ecotoxicology														
Acute/Prolonged Toxicity to Fish	96-h LC_{50} (bluegill sunfish): 75 mg/L 96-h LC_{50} (mosquito fish): 251 mg/L	Price et al. 1974 Wallen et al. 1957	96-h LC50 (fathead minnow): 79-88 mg/L 96-h LC_{50} (mosquito fish): 238 mg/L	Mattson et al. 1976 Jones 1971	--		--		--		96-h LC_{50} (rainbow trout): 6,100 mg/L	Huntingdon Research Center 1992	96-h LC_0 (zebra fish): >100 mg/L 5-d LC_{50} (fathead minnow embryos): 13.3 mg/L	Huels 1993 DeYoung et al. 1996
Acute Toxicity to Daphnia	24-h (@ pH 7): 6,000 mg/L 48-h EC_{50}: 65 mg/L	Bringmann and Kuhn 1982 Janssen et al. 1993	--		--		--		--		--		24-h LC50: 7,170 mg/L 48-h EC_{50}: > 1,000 mg/L	Bringmann and Kuhn 1977 Huels 1993
Toxicity to Aquatic Plants (e.g., algae)	8-day, growth inhibition test; toxicity threshold = 4,000 mg/L	Bringmann and Kuhn 1980	--		--		--		--		--		Growth inhibition in photoautotrophic algae @ 2,460 mg/L after 60-h	Hoare et al. 1967
Toxicology														
Acute Oral Toxicity	LD_{50} (mouse): 4,960 mg/kg bw	Woodward et al. 1941	--		LD_{50} (rat): 4,280 mg/kg bw	Smyth et al. 1969	LD_{50} (rat): 8,610 mg/kg bw	Green 1977	LD_{50} (rat): 3,730 mg/kg bw	Smyth et al. 1969	LD_{50} (rat): 3,250 mg/kg bw	Smyth et al. 1969	LD_{50} (rat): 3,530 mg/kg bw	Lewis 1994
Acute Inhalation Toxicity	4-h LC_{50} (rat): 11.4 mg/L > 1,000 ppm in mice produced irritation of the conjunctiva and upper respiratory tract	BASF 1989 Ghiringhelli and Difabio 1957	--		--		--		--		--		LC_{50} (rat): > 30 g/m^3	BIOFAX 1971
Acute Dermal Toxicity	LD_{50} (rabbit): 1,060 mg/kg bw	Union Carbide 1963	--		--		--		--		--		--	
Acute Toxicity by Other Routes	LD_{50} (i.v.; mouse): 525 mg/kg bw	Oro and Wretlind 1961	LD_{50} (i.p.; rat): 632 mg/kg LD_{50} (i.v. mouse): 98 mg/kg	Lewis 1994 Lewis 1994	LD_{50} (i.v.; mouse): 52 mg/kg bw	Welch et al. 1944	LD_{50} (I.v., mouse): 111 mg/kg bw	RTECS 2000	--		--		s.c. LD_{50} (mouse): 3,200 mg/kg bw	Allen et al. 1986

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Description	Acetic Acid	Source	Acetic Acid, Ammonium Salt	Source	Acetic Acid, Calcium Salt	Source	Acetic Acid, Magnesium Salt	Source
Structure								
CAS Number	64-19-7		631-61-8		62-54-4		142-72-3	
Physical-Chemical Properties								
Structural Formula	$H_4C_2O_2$		$H_7C_2NO_2$		$H_6CaC_4O_4$		$C_4H_6MgO_4$	
Melting Point	16.7°C	Verschueren 1996	114°C	Verschueren 1996	--		80°C	Budavari 1996
Boiling Point	118.1°C	Verschueren 1996	--		Decomposes above 160°C	Budavari 1996	--	
Vapour Pressure	11.4 mm Hg @ 20°C	Verschueren 1996	1.31 x 10^{-4} mm Hg @ 25°C	USEPA 2000 (calculated)	5.48 x 10^{-3} mm Hg @ 25°C	USEPA 2000 (calculated)	--	
Octanol/Water Partition Coefficient (log)	-0.17	Verschueren 1996	-2.79	USEPA 2000 (calculated)	-1.38	USEPA 2000 (calculated)	-1.38	USEPA 2000 (calculated)
Water Solubility	50 g/L @ 20°C	Verschueren 1996	1,480 g/L @ 4°C	Lide 1999	430 g/L @ 25°C	Verdugt 1992	Very soluble in water or alcohol	Budavari 1996
pH Value, pKa Value	pH: 2.5 at 50 g/L and 20°C pKa: 4.76 @ 25°C	Hoescht 1994 Serjeant and Dempsey 1979	pH: 7.0 @ 350 g/L	Budavari 1996	pH: 7.6 @ 32 g/L	Budavari 1996	--	
Fate and Transport								

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Description	Acetic Acid	Source	Acetic Acid, Ammonium Salt	Source	Acetic Acid, Calcium Salt	Source	Acetic Acid, Magnesium Salt	Source
Photodegradation	$5.1x10^{-13}$ cm^3/molecule*sec 50% degradation after 21 days	Hoechst 1994 (calculated)	--		--		--	
Stability in Water	Acids dissociate in water		Salts dissociate in water		Salts dissociate in water		Salts dissociate in water	
Biodegradation	Readily biodegradable: 99% after 7 days under anaerobic conditions using activated sludge	Kameya T. et al. 1995	Biodegrades in days to weeks	USEPA 2000 (calculated)	Readily biodegrades under aerobic conditions using activated sludge	Lohmann Unpublished	--	

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Description	Acetic Acid	Source	Acetic Acid, Ammonium Salt	Source	Acetic Acid, Calcium Salt	Source	Acetic Acid, Magnesium Salt	Source
Ecotoxicology								
Acute/Prolonged Toxicity to Fish	96-h LC_{50} (bluegill sunfish): 75 mg/L 96-h LC_{50} (mosquito fish): 251 mg/L	Price et al. 1974 Wallen et al. 1957	96-h LC50 (fathead minnow): 79-88 mg/L 96-h LC_{50} (mosquito fish): 238 mg/L	Mattson et al. 1976 Jones 1971	--		--	
Acute Toxicity to Daphnia	24-h (@ pH 7): 6,000 mg/L 48-h EC_{50}: 65 mg/L	Bringmann and Kuhn 1982 Janssen et al. 1993	--		--		--	
Toxicity to Aquatic Plants (e.g., algae)	8-day, growth inhibition test; toxicity threshold = 4,000 mg/L	Bringmann and Kuhn 1980	--		--		--	
Toxicology								
Acute Oral Toxicity	LD_{50} (mouse): 4,960 mg/kg bw	Woodward et al. 1941	--		LD_{50} (rat): 4,280 mg/kg bw	Smyth et al. 1969	LD_{50} (rat): 8,610 mg/kg bw	Green 1977
Acute Inhalation Toxicity	4-h LC_{50} (rat): 11.4 mg/L > 1,000 ppm in mice produced irritation of the conjunctiva and upper respiratory tract	BASF 1989 Ghiringhelli and Difabio 1957	--		--		--	
Acute Dermal Toxicity	LD_{50} (rabbit): 1,060 mg/kg bw	Union Carbide 1963	--		--		--	
Acute Toxicity by Other Routes	LD_{50} (i.v.; mouse): 525 mg/kg bw	Oro and Wretlind 1961	LD_{50} (i.p.; rat): 632 mg/kg LD_{50} (i.v. mouse): 98 mg/kg	Lewis 1994 Lewis 1994	LD_{50} (i.v.; mouse): 52 mg/kg bw	Welch et al. 1944	LD_{50} (I.v., mouse): 111 mg/kg bw	RTECS 2000

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

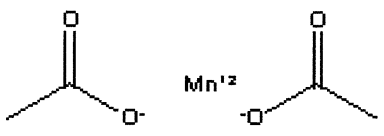
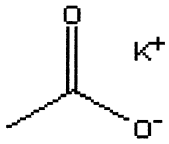
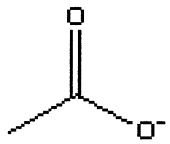
Description	Acetic Acid	Source	Acetic Acid, Ammonium Salt	Source	Acetic Acid, Calcium Salt	Source	Acetic Acid, Magnesium Salt	Source
Repeated Dose Toxicity	Induced hyperplasia in rats @ 60 mg/kg bw (oral; 3 times/wk for 8 mo) Increased spleen and kidney weights, kidney damage @ 23-31 mg/kg bw (inhalation; continuous 3-35 d)	Alexandrov et al. 1989 Savina and Anisimov 1987	--		--		--	
Genetic Toxicity *in vitro* (Bacterial test)	Negative Negative Negative	McMahon et al. 1979 Zeiger et al. 1992 BIBRA 1993	--		--		--	
Genetic Toxicity *in vitro* (Non-bacterial test)	Cytotoxic due to low pH, not clastogenic	Morita et al. 1990	--		--		--	
Genetic Toxicity *in vivo*	--		--		--		--	
Toxicity to Reproduction	--		--		--		--	

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Description	Acetic Acid	Source	Acetic Acid, Ammonium Salt	Source	Acetic Acid, Calcium Salt	Source	Acetic Acid, Magnesium Salt	Source
Developmental Toxicity/Teratogenicity	No effects on nidation or on maternal or fetal survival in mice, rats, and rabbits at oral doses up to 1600 mg/kg bw/day	FDRL 1974	--		--		--	

Notes:
i.v. = intravenous
i.p. = intraperitoneal
s.c. = subcutaneous
-- = Data unavailable

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Acetic Acid, Manganese Salt	Source	Acetic Acid, Potassium Salt	Source	Acetic Acid, Sodium Salt	Source
					
638-38-0		127-08-2		127-09-3	
$C_4H_6MnO_4$		$H_3KC_2O_2$		$H_3NaC_2O_2$	
--		292°C	Lewis 1994	58°C	Lewis 1994
--		--		Decomposes above 400°C	Hoechst 1993
--		1.37×10^{-8} mm Hg @ 25°C	USEPA 2000 (calculated)	5.39×10^{-9} mm Hg @ 25°C	USEPA 2000 (calculated)
-0.58	USEPA 2000 (calculated)	-3.72	USEPA 2000 (calculated)	-3.72	USEPA 2000 (calculated)
Soluble in water or alcohol	Budavari 1996	2,530 g/L	Lewis 1994	365 g/L @ 20°C	Hoechst 1993
--		pH: 9.7 @ 98 g/L	Budavari 1996	pH: 7.5-9 @ 50 g/L , 20°C	Hoechst 1993

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Acetic Acid, Manganese Salt	Source	Acetic Acid, Potassium Salt	Source	Acetic Acid, Sodium Salt	Source
--		--		6.6% photomineralization after 17-h UV irradiation (> 290 nm)	Freitag et al. 1985
Salts dissociate in water		Salts dissociate in water		Salts dissociate in water	
--		--		Inherently biodegradable: 100% after 5 days @ 160 mg/L under aerobic conditions using activated sludge Inherently biodegradable: 52.6% after 5 days @ 0.05 mg/L under aerobic conditions using activated sludge	Huels unpublished Freitag et al. 1985

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Acetic Acid, Manganese Salt	Source	Acetic Acid, Potassium Salt	Source	Acetic Acid, Sodium Salt	Source
--		96-h LC_{50} (rainbow trout): 6,100 mg/L	Huntingdon Research Center 1992	96-h LC_0 (zebra fish): >100 mg/L 5-d LC_{50} (fathead minnow embryos): 13.3 mg/L	Huels 1993 DeYoung et al. 1996
--		--		24-h LC50: 7,170 mg/L 48-h EC_{50}: > 1,000 mg/L	Bringmann and Kuhn 1977 Huels 1993
--		--		Growth inhibition in photoautotrophic algae @ 2,460 mg/L after 60-h	Hoare et al. 1967
LD_{50} (rat): 3,730 mg/kg bw	Smyth et al. 1969	LD_{50} (rat): 3,250 mg/kg bw	Smyth et al. 1969	LD_{50} (rat): 3,530 mg/kg bw	Lewis 1994
--		--		LC_{50} (rat): > 30 g/m^3	BIOFAX 1971
--		--		--	
--		--		s.c. LD_{50} (mouse): 3,200 mg/kg bw	Allen et al. 1986

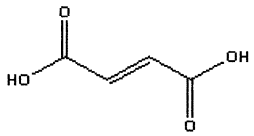
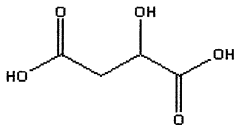
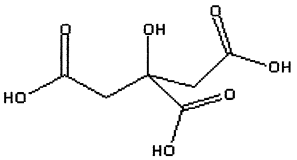
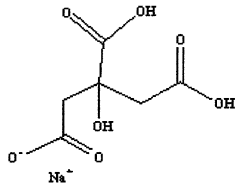
APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Acetic Acid, Manganese Salt	Source	Acetic Acid, Potassium Salt	Source	Acetic Acid, Sodium Salt	Source
Body weight gain suppressed, changes in spontaneous motor activity, and decrease in dopamine in the hypothalamus of young male mice fed 2 g Mn/kg of food for 1 year	Komura and Sakamoto 1992	--		NOAEL (drinking water; rat; 8 mo): 500 mg/L Normal growth and survival in rats @ 3.6 g/kg bw/day (4 wks;daily oral) No cognitive impairment in young rats @ 100 mg/kg bw/day (112 d;continuous drinking water) Altered thyroid function, decreased growth @ 21 mgkg bw/d (oral; daily)	Cory-Slechta 1986 Dryden and Hartman 1971 Massaro and Massaro 1987 Goldman 1981
Weakly positive (rec-assay using *Bacillus subtillus*)	Nishioka 1975	--		Negative Negative	BIBRA 1993 Ishidate et al. 1984
--		--		Negative	Ishidate et al. 1984
--		--		No inhibitory effect on DNA-replication detectable	Seiler 1981
--		--		--	

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Acetic Acid, Manganese Salt	Source	Acetic Acid, Potassium Salt	Source	Acetic Acid, Sodium Salt	Source
Abnormalities occurred in birds at 1.47 mg/egg when injected into the air cell of eggs at 96 hrs	Verret et al. 1980	--		No maternal or neonatal effects in mice @ 1,000 mg/kg bw Nonteratogenic to chick embryos @10 mg/egg	Kavlock et al. 1987 Verret et al. 1980

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Description	Fumaric Acid	Source	Malic Acid	Source	Citric Acid	Source	Citric Acid, Sodium Salt	Source
Structure								
CAS Number	110-17-8		6915-15-7		77-92-9		994-36-5	
Physical-Chemical Properties								
Structural Formula	$H_4C_4O_4$		$H_6C_4O_5$		$H_8C_6O_7$		$H_7NaC_6O_7$	
Melting Point	287°C	Verschueren 1996	128°C	Lewis 1994	153°C	Verschueren 1996	--	
Boiling Point	290°C (sublimes)	Verschueren 1996	Decomposes above 140°C	Lewis 1994	Decomposes	Verschueren 1996	--	
Vapour Pressure	$1.54x10^{-4}$ mm Hg @ 25°C	Verschueren 1996	2.93×10^{-6} mm Hg @ 25°C	USEPA 2000 (calculated)	5.64×10^{-9} mm Hg @25°C	USEPA 2000 (calculated)	--	
Octanol/Water Partition Coefficient (log)	0.33 @ 23°C	Verschueren 1996	-1.26	Hansch and Leo 1987	-1.72	Verschueren 1996	-0.28	USEPA 2000 (calculated)
Water Solubility	7 g/l @ 25°C	Verschueren 1996	592 g/L @25°C	Yalkowsky 1989	1,330 g/L @ 20°C	Verschueren 1996	--	
pH Value, pKa Value	pH: 2.1 @ 5 g/L; 20°C pK1: 3.02; pK2: 4.46 @ 18°C	Weast 1988	pK1: 3.40; pK2: 5.05	Clayton and Clayton 1994	pH: 2.2 at 0.1 N solution pK1: 3.13; pK2: 4.76; pK3: 6.40	Budavari 1996	--	
Fate and Transport								

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Description	Fumaric Acid	Source	Malic Acid	Source	Citric Acid	Source	Citric Acid, Sodium Salt	Source
Photodegradation	$5.3x10^{-12}$ cm^3/molecule*sec 50% after 7.3 hours	Atkinson 1987	Photolysis rate of $7.76x10^{12}$ cm^3/mole*sec at 25C; 50% after 2 days	Meylan and Howard 1993	--		--	
Stability in Water	Half-life in natural waters was 1-15 days	Saito and Nagao 1978	Biodegrades readily in water	Fournier et al. 1992	Acids dissociate in water		Salts dissociate in water	
Biodegradation	Readily biodegradable: 98% after 21 days under aerobic conditions using predominantly domestic sewage	Huels 1992	--		Readily biodegradable: 98% after 48-h under aerobic conditions using domestic sewage	European Commission 1996	--	

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Description	Fumaric Acid	Source	Malic Acid	Source	Citric Acid	Source	Citric Acid, Sodium Salt	Source
Ecotoxicology								
Acute/Prolonged Toxicity to Fish	48-h LC_{50} (zebra fish): 245 mg/L	Huels 1992	--		96-h LC_{50} (bluegill sunfish): 1,516 mg/L	Schwartz and Davis 1973	--	
Acute Toxicity to Daphnia	48-h EC_{50}: 212 mg/L	Randall and Knopp 1980	48-h LC_{50}: 240 mg/L	Forbis 1989	24-h EC50: 1535 mg/L 72-h EC_{50}: 120 mg/L	Bringmann and Kuhn 1982 Ellis 1937	--	
Toxicity to Aquatic Plants (e.g., algae)	72-h EC_{50} (green algae): 41 mg/L	AIDA 1988	--		8-day growth inhibition test, toxicity threshold: 640 mg/L	Bringmann and Kuhn 1980	--	
Toxicology								
Acute Oral Toxicity	LD_{50} (rat): 9,300 mg/kg bw (female); 10,700 mg/kg bw (male) LD_{50} (rat): 10,000 mg/kg bw	Vernot et al. 1977 Ullman's	LD_{50} (mouse, rat): 1,600-3,200 mg/kg bw	Eastman Kodak 1981	LD_{50} (rat): 11,700 mg/kg bw LD_{50} (mouse): 5,790 mg/kg bw	Yokotani et al. 1971	LD_{50} (mouse): 7,100 mg/kg bw	Oelkers 1965
Acute Inhalation Toxicity	--		--		--		--	
Acute Dermal Toxicity	LD_{50} (rabbit): >20,000 mg/kg bw	Vernot et al. 1977	--		4-h exposure caused erythema and edema in rabbits.	Hill Top Biolabs, Inc. 1992	--	
Acute Toxicity by Other Routes	Hepatotoxicy in rats @ 10 mg/kg via i.p. LD_{50} (i.p., mouse): 200 mg/kg bw	Mileski et al. 1965 Smith et al. 1963	LD_{50} (i.p., mouse): 100 mg/kg	Eastman Kodak 1981	LD50 = 2,700-5,500 mg/kg (s.c., rat)	Yokotani et al. 1971	No cardiovascular effects in horses given i.v. LD_{50} (i.p.; rat): 1,348 mg/kg bw LD_{50} (i.p.; mouse): 1,635 mg/kg bw	Hubbell et al. 1987 Lewis 1994 Lewis 1994

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

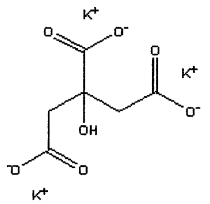
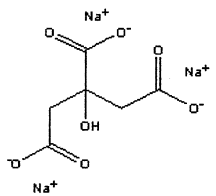
Description	Fumaric Acid	Source	Malic Acid	Source	Citric Acid	Source	Citric Acid, Sodium Salt	Source
Repeated Dose Toxicity	Slightly increased mortality and increased incidence of testes degeneration in rats fed diet @ 750 mg/kg bw (daily for 2 yrs)	Fitzhugh and Nelson 1947	Changes in organ weights, deceased growth, hunched appearance in rats @ 200 mg/kg bw (daily for 2 yrs)	Hazleton Laboratories 1971	No gross or histopathological changes or effects on growth or survival @ 5% (oral; daily; 150 d) NOEL (oral feed; 6wks; rat): 2,260 mg/kg bw; LOAEL (oral feed; 6 wks; rat): 4,670 mg/kg bw	Packman et al. 1963 Yokotani et al. 1971	No adverse effects in 2 generations of rats fed sodium citrate as 0.1% of diet daily No adverse effects in male rats over 32 week daily oral exposure @ 2,500 mg/kg bw	Bonting and Jansen 1956 Fukushima et al. 1986
Genetic Toxicity in-vitro (Bacterial test)	Negative Negative	BIBRA 1991 Rapson et al. 1980	Negative	Al-Ani and Al-Lami 1988	Negative	Al-Ani and Al-Lami 1988	Negative Negative	Litton Bionetics Inc. 1975 Ishidate et al. 1984
Genetic Toxicity in-vitro (Non-bacterial test)	Negative	Ishidate et al. 1984	Negative	Ishidate et al. 1984	--		--	
Genetic Toxicity in-vivo	--		--		Not mutagenic	Litton Bionetics 1975	--	
Toxicity to Reproduction	No evidence of reproductive toxicity @ 400 mg/kg bw	Levey et al. 1946	--		NOAEL (oral feed; rat): = 600 mg/kg bw No effects on reproductive parameters at 5% (oral feed; rat, mouse), but effected body weight gain and survival time in adults	Bonting and Jansen 1956 Wright and Hughes 1976	No reproductive effects in rats fed 0.1% sodium citrate in diet	Bonting and Jansen 1956

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Description	Fumaric Acid	Source	Malic Acid	Source	Citric Acid	Source	Citric Acid, Sodium Salt	Source
Developmental Toxicity/Teratogenicity	No apparent teratogenic effect	Bournias-Vardiabasis 1983	Nonteratogenic to chick embryos at up to 10 mg/egg No treatment-related fetal or maternal toxic effects observed @ up to 350 mg/kg bw (oral; daily; rats, mice)	Verrett et al. 1980 FDRL 1974	No maternal or fetal effects @ 241 mg/kg bw	FDRL 1973	Nonteratogenic to chick embryos @ 10 mg/egg	Verrett et al. 1980

Notes:
i.v. = intravenous
i.p. = intraperitoneal
s.c. = subcutaneous
-- = Data unavailable

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Citric Acid, Tripotassium Salt	Source	Citric Acid, Trisodium Salt	Source
			
866-84-2		68-04-2	
$H_5K_3C_6O_7$		$H_5Na_3C_6O_7$	
211°C	USEPA 2000 (calculated)	150°C	European Commission 1996
Decomposes when heated to 230°C	Lewis 1994	Decomposes at red heat	Lewis 1994
$2.09x10^{-12}$ mm Hg @ 25°C	USEPA 2000 (calculated)	$2.09x10^{-12}$ mm Hg @ 25°C	USEPA 2000 (calculated)
-0.28	USEPA 2000 (calculated)	-0.28	USEPA 2000 (calculated)
63 g/L	USEPA 2000 (calculated)	~425 g/L @ 25°C	European Commission 1996
--		pH: ~8	Budavari 1996

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Citric Acid, Tripotassium Salt	Source	Citric Acid, Trisodium Salt	Source
--		--	
Salts dissociate in water		Salts dissociate in water	
--		Readily biodegradable: 90% after 30 d under aerobic conditions using activated sludge	Henkel unpublished

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Citric Acid, Tripotassium Salt	Source	Citric Acid, Trisodium Salt	Source
--		96-h LC50 (guppy, medaka): > 18,000- 32,000 mg/L	Sloof and Kappers 1982
--		48-h EC_{50}: 5,600-10,000 mg/L	Sloof and Kappers 1982
--		96-h EC_{50} (algae): > 18,000-32,000 mg/L	Sloof and Kappers 1982
--		--	
--		--	
--		--	
LD_{50} (i.v. dog): 167 mg/kg bw	Lewis 1994	LD_{50} (i.p., rat): 1,548 mg/kg bw LD_{50} (i.p., mouse): 1,364 mg/kg bw LD_{50} (i.v., mouse): 170 mg/kg bw LD_{50} (i.v., rabbit): 449 mg/kg bw	RTECS 1999

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Citric Acid, Tripotassium Salt	Source	Citric Acid, Trisodium Salt	Source
--		--	
Negative	Litton 1975	--	
--		--	
--		--	
--		--	

APPENDIX 1
SUMMARY DATA TABLE FOR CARBOXYLIC FOOD ACIDS AND SALTS CATEGORY

Citric Acid, Tripotassium Salt	Source	Citric Acid, Trisodium Salt	Source
--		--	

APPENDIX 1
SUMMARY DATA TABLE FOR ACETIC ACID AND SALTS CATEGORY

Description	Acetic Acid	Source	Acetic Acid, Ammonium Salt	Source	Acetic Acid, Calcium Salt	Source	Acetic Acid, Magnesium Salt	Source	Acetic Acid, Manganese Salt	Source	Acetic Acid, Potassium Salt	Source	Acetic Acid, Sodium Salt	Source
Repeated Dose Toxicity	Induced hyperplasia in rats @ 60 mg/kg bw (oral; 3 times/wk for 8 mo) Increased spleen and kidney weights, kidney damage @ 23-31 mg/kg bw (inhalation; continuous 3-35 d)	Alexandrov et al. 1989 Savina and Anisimov 1987	--		--		--		Body weight gain suppressed, changes in spontaneous motor activity, and decrease in dopamine in the hypothalamus of young male mice fed 2 g Mn/kg of food for 1 year	Komura and Sakamoto 1992	--		NOAEL (drinking water; rat; 8 mo): 500 mg/L Normal growth and survival in rats @ 3.6 g/kg bw/day (4 wks;daily oral) No cognitive impairment in young rats @ 100 mg/kg bw/day (112 d;continuous drinking water) Altered thyroid function, decreased growth @ 21 mgkg bw/d (oral; daily)	Cory-Slechta 1986 Dryden and Hartman 1971 Massaro and Massaro 1987 Goldman 1981
Genetic Toxicity *in vitro* (Bacterial test)	Negative Negative Negative	McMahon et al. 1979 Zeiger et al. 1992 BIBRA 1993	--		--		--		Weakly positive (rec-assay using *Bacillus subtillus*)	Nishioka 1975	--		Negative Negative	BIBRA 1993 Ishidate et al. 1984
Genetic Toxicity *in vitro* (Non-bacterial test)	Cytotoxic due to low pH, not clastogenic	Morita et al. 1990	--		--		--		--		--		Negative	Ishidate et al. 1984
Genetic Toxicity *in vivo*	--		--		--		--		--		--		No inhibitory effect on DNA-replication detectable	Seiler 1981
Toxicity to Reproduction	--		--		--		--		--		--		--	
Developmental Toxicity/Teratogenicity	No effects on nidation or on maternal or fetal survival in mice, rats, and rabbits at oral doses up to 1600 mg/kg bw/day	FDRL 1974	--		--		--		Abnormalities occurred in birds at 1.47 mg/egg when injected into the air cell of eggs at 96 hrs	Verret et al. 1980	--		No maternal or neonatal effects in mice @ 1,000 mg/kg bw Nonteratogenic to chick embryos @10 mg/egg	Kavlock et al. 1987 Verret et al. 1980

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